Proteomic analyses reveal misregulation of LIN28 expression and delayed timing of glial differentiation in human iPS cells with MECP2 loss-of-function.

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Public Summary:
Rett syndrome is a severe neurological disorder caused by mutations in the MECP2 gene. The mutated gene can affect neurons and astrocytes, two important cell types in the brain. Here we showed that the gene is also important for the timing when these two cell types originated in the brain. We also found that this misregulation is caused by alterations in the LIN28 pathway, important for cell fate decision. The work reveals a novel role of MECP2 during development that might contribute and explain some clinical symptoms observed in affected individuals.

Scientific Abstract:
Rett syndrome (RTT) is a pervasive developmental disorder caused by mutations in MECP2. Complete loss of MECP2 function in males causes congenital encephalopathy, neurodevelopmental arrest, and early lethality. Induced pluripotent stem cell (iPSC) lines from male patients harboring mutations in MECP2, along with control lines from their unaffected fathers, give us an opportunity to identify some of the earliest cellular and molecular changes associated with MECP2 loss-of-function (LOF). We differentiated iPSC-derived neural progenitor cells (NPCs) using retinoic acid (RA) and found that astrocyte differentiation is perturbed in iPSC lines derived from two different patients. Using highly stringent quantitative proteomic analyses, we found that LIN28, a gene important for cell fate regulation and developmental timing, is upregulated in mutant NPCs compared to WT controls. Overexpression of LIN28 protein in control NPCs suppressed astrocyte differentiation and reduced neuronal synapse density, whereas downregulation of LIN28 expression in mutant NPCs partially rescued this synaptic deficiency. These results indicate that the pathophysiology of RTT may be caused in part by misregulation of developmental timing in neural progenitors, and the subsequent consequences of this disruption on neuronal and glial differentiation.